

II. RESPONSE TO OFFICIAL ACTION OF DECEMBER 29, 2005

A. Status of the Claims

Claims 1, 2, 4, 6-8, 10-12, 14, 15, and 18-23 were pending in the case at the time of the Official Action (“Action”), dated December 29, 2005. All claims stand rejected. Claims 1, 2, 4, 6-8, 10-12, 14, 15, and 18-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brodack et al. (U.S. Patent No. 5,560,901).

B. Summary of Examiner Interview On March 23, 2006

On March 23, 2006, the Examiner graciously granted a telephone interview with Margaret Sampson and Michael Samardzija to discuss the present application.

During the interview, Applicant pointed out to the Examiner that Brodack et al. (“Brodack”) does not disclose particles comprising a coprecipitate of a metal and one or more radioactive isotopes. The Examiner indicated that she would consider this argument in light of the additional information submitted in the Response to the Action.

C. Rejection Based on Brodack et al Under 35 U.S.C. § 103(a) Are Overcome

Claims 1, 2, 4, 6-8, 10-12, 14, 15, and 18-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Brodack. The Action argues that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a radiopharmaceutical composition having particles comprising a metal and one or more radioactive isotopes because Brodack et al discloses radionuclide labeled particles that meet the limitations of the instant invention... . Thus, one would be motivated to select the various components and specific elements of Applicant’s elected species because the species components are each disclosed in the listings of Brodack et al.” Action, p. 3.

Applicant respectfully traverses this rejection because Brodack does not disclose particles comprising a coprecipitate of a metal and one or more radioactive isotopes, and teaches away

from such particles. Surprisingly, the coprecipitation of a metal with one or more radioactive isotopes can concentrate the radioactive isotopes up to 100 fold in the particles generated. This concentration of the radioactive isotopes allows for the production of therapeutic radiopharmaceutical macroaggregate compositions in sufficiently small volumes for practical use. In addition, the compositions can be carrier-free. This surprising feature of the coprecipitates disclosed in Applicant's pending application are neither found in nor suggested by Brodack.

Brodack discloses compositions for radiation synovectomy. Brodack states that a problem of the prior art is "unacceptable radiation doses to non-target organ systems due to leakage of radioactive material from the cavity," which may be due to "lack of a tight binding of the nuclide to the particle." Brodack, col. 1, ll. 46-57. Thus, "binding between the radionuclide and the particle should be essentially irreversible through the course of radiotherapy." *Id.* at col. 2, ll. 8-10. To achieve the "essentially irreversible" binding of the radionuclide and the particle, Brodack discloses the use of suitable ligands for complexing the radionuclide with the particles. *Id.* at col. 4, ll. 54-59. As explained by Brodack: "The radiation agent of this invention can be prepared by attaching or binding to the particle the desired isotope under standard conditions for attachment. This involves coupling a ligand (either with or without a radioactive atom) to the particle..." *Id.* at col. 5, ll. 29-34. The coupling portion of the ligand may be able to "easily and specifically bind covalently to functional groups on the particle or [] may simply adsorb very strongly to the surface of the particle." *Id.* at ll. 37-40.

Brodack describes two methods for preparing desired radiation synovectomy agents. *Id.* at col. 5, l. 50-col. 6, l. 4. The first method links a radionuclide, which has been incorporated into a ligand, directly to the particle by covalent bonding, while the second method links the ligand to the particle by covalent bonding, and the radionuclide is incorporated into the

coordinated bonded complexing ligand. *Id.* Thus, the methods disclosed in Brodack for preparing radiation synovectomy compositions involve directly manipulating the molecules themselves. Brodack does not disclose the method of coprecipitation, or coprecipitate particles.

The presently claimed subject matter is directed to a radiopharmaceutical macroaggregate composition comprising particles, which comprise a coprecipitate of a metal and one or more radioactive isotopes. These coprecipitates are formed by alkalization of soluble metal and radioactive isotope(s) to an appropriate pH to separate a coprecipitate of the metal and isotope(s) from the solution. This method is very different than the methods of preparation disclosed in Brodack. In addition, the resulting coprecipitates are different than the compositions disclosed in Brodack, in which the molecules themselves are manipulated to generate the disclosed compositions, for example by the activation of multiple organic moieties. *Id.* at col. 5, ll. 30-45.

In addition, Brodack states that the particles of its disclosure are preferably “not prone to aggregation under the conditions used to prepare or store the radiation synovectomy agent.” *Id.* at col. 3, ll. 7-10. In contrast, the present claims are directed to radiopharmaceutical *macroaggregate* compositions, i.e., compositions formed by aggregation. These compositions comprise particles, which in turn comprise coprecipitates of a metal and one or more radioactive isotopes formed by aggregation. Therefore, Brodack in fact teaches one of skill in the art away from the presently claimed compositions, which are prepared by aggregation.

Another reference, Crawford *et al.*, Langmuir 9:3050-56 (1993) (attached hereto as Exhibit A), may elucidate the mechanism behind the therapeutic value of Applicant's radiopharmaceutical macroaggregate compositions, which can concentrate a high level of radioactive isotopes in a small volume. Crawford examined coprecipitation versus absorption with amorphous iron-(III) oxide colloids, and demonstrated the different characteristics of the resulting compositions. For example, Crawford found that coprecipitation removal of metal ions

using iron oxide colloids is greater than that achieved by adsorption alone. Crawford, p. 3056. Applicant notes that Crawford does not disclose radionuclides, and that iron oxide is a colloid, whereas a soluble metal such as a metal chloride and a soluble radioactive isotope(s) are used to form a coprecipitate in Applicant's disclosure.

Although not wishing to be bound by any particular theory, it is possible that the coprecipitates of a metal and one or more radioactive isotopes disclosed in the present application are based on the mechanism elucidated in Crawford, which is quite distinct from the mechanism disclosed in Brodack, and necessarily results in distinct compositions. This mechanism may explain why a coprecipitate of a metal and one or more radioactive isotopes can result in enhanced concentration of the radioactive isotope(s) in the coprecipitate. While the mechanism and experiments of Crawford did not use nanomolar ranges of reactants, the present application discloses coprecipitates generated using nanomolar ranges of radioactive isotope(s), as well as carrier-free compositions. This ability to generate particles comprising coprecipitates of a metal and one or more radioactive isotopes in no-carrier-added forms would have been surprising to one of skill in the art. For example, both Colombetti *et al.*, *J Nucl Med* 11: 704-707 (1970) and Stern *et al.*, *Nucleonics* 24(10):57-59 (1966) describe deliberate efforts to generate coprecipitates by adding non-radioactive forms of the radionuclide, which led to compositions with unacceptable levels of toxicity.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be a suggestion or motivation to combine the reference teachings either in the references themselves or in the general knowledge of one of ordinary skill in the art; (2) there must be a reasonable expectation of success; and (3) the references when combined must teach or suggest all the claim limitations. MPEP §§ 2142 & 2143. Brodack only discloses two specific methods of preparing radiation synovectomy compositions, does not disclose or suggest

the method of coprecipitation or the generation of coprecipitates, and in fact teaches away from such aggregation compositions. Therefore, Brodack cannot establish a *prima facie* case of obviousness of the presently pending claims because it does not teach or suggest the claimed subject matter, does not create any reasonable expectation that the claimed subject matter would work, and does not teach or suggest all of the claim limitations.